REMARKS

Amendments to the Claims

Claim 1 is amended to recite that the alphavirus vector is a chimeric alphavirus particle containing a Venezuelan Equine Encephalitis (VEE) virus vector construct packaged with Sindbis (SIN) virus envelope glycoproteins. Support is at Example 8 on pages 51-52.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 5, 8-10, 13-15, 19-21, 29, 30, 35-39, 41, and 42 stand rejected under 35 U.S.C. § 103(a) as obvious over Malone[1] in view of Barchfield[2] as evidenced by Rappuoli.[3]

Malone is cited as teaching intranasal administration of replication-deficient alphaviral vectors and adjuvants. Barchfield is cited as teaching detoxified bacterial toxins. The Office Action contends it would have been obvious to substitute the adjuvant of Malone with the adjuvants of Barchfield to enhance the immune response induced by Malone's composition, and that Rappuoli teaches detoxified bacterial ADP-ribosylating toxins would work as mucosal adjuvants. See Office Action at page 3 and non-final Office Action of October 15, 2010.

To advance prosecution, claim 1 is amended to recite that the alphavirus vector is a chimeric alphavirus particle containing a Venezuelan Equine Encephalitis (VEE) virus vector construct packaged with Sindbis (SIN) virus envelope glycoproteins. Claims 13-15, 29, and 30 are canceled.

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[1] U.S. Patent No. 6,110,898.
[2] WO 98/42375.
[3] WO 95/17211.

A *prima facie* case of obviousness requires at least a suggestion of all limitations in a claim. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)(citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)).

None of the cited references, alone or in combination, teaches or suggests an alphavirus vector that is a chimeric alphavirus particle containing a Venezuelan Equine Encephalitis (VEE) virus vector construct packaged with Sindbis (SIN) virus envelope glycoproteins. Malone teaches "chimeric viral vectors," col. 3, lines 54-57, but provides no teaching or suggestion to select a VEE virus vector construct with Sindbis virus envelope glycoproteins for combination in a replicon particle.

Secondary considerations such as unexpected results and important advantages are relevant as indicia of non-obviousness, *Graham v. John Deere* Co. *of Kansas City*, 383 U.S. 1, 17-18 (1966), and must be considered in a determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

Here, one of ordinary skill in the art would not have expected the improved immune responses obtained with the claimed method. Figure 13 compares immune responses obtained following intranasal administration of four different vectors, each expressing the same HIV gag antigen. Two vectors, SIN-gag and VEE-gag, are non-chimeric vectors. The remaining two, SIN/VEE-gag and VEE/SIN-gag, are both chimeric vectors. SIN/VEE-gag is a SIN virus vector construct packaged with SIN virus envelope glycoproteins. VEE/SIN-gag is a VEE virus vector construct packaged with SIN virus envelope glycoproteins, as recited in claim 1.

As shown in Fig. 13, the non-chimeric replicon particles SIN-gag and VEE-gag induced comparable numbers of IFNγ-secreting cells per 10^7 mononuclear cells ("10 mill

MNC" in Fig. 13). The SIN/VEE-gag replicon particles induced less than 500 IFNγ-secreting cells per 10^7 mononuclear cells, demonstrating that this chimeric replicon particle is much less potent than the non-chimeric particles.

In contrast, the response induced by VEE/SIN-gag was strikingly more potent than the next best response, demonstrating that the VEE/SIN-gag particle is particularly effective at inducing immune responses when administered intranasally. Nothing in the cited art would have led the skilled artisan to expect that administering a VEE virus vector construct packaged with SIN virus envelope glycoproteins would provide such a robust immune response.

None of the references, alone or in combination, teaches all elements of claim 1. The Patent Office has therefore not made a *prima facie* claim of obviousness with respect to claim 1 or dependent claims 5, 8-10, 19-21, 35-39, 41, and 42. Moreover, even assuming a *prima facie* case had been made, the unexpectedly robust immune response obtained using the recited method rebuts the *prima facie* case.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1 and 41 Under 35 U.S.C. § 103(a)

Claims 1 and 41 stand rejected as obvious over Malone, Barchfield, Rappuoli, and McCluskie. McCluskie[4] is added to the asserted combination of Malone, Barchfield, and Rappuoli to reject claims 1 and 41 as obvious.

[4] McCluskie *et al.*, "Cutting Edge: Cpg DNA is a potent enhancer of systemic and mucosal immune responses against hepatitis B surface antigen with intranasal administration to mice." J. Immunol. 1998 161:4463-4466.

The deficiencies of Malone, Barchfield, and Rappuoli are discussed above. McCluskie is cited as teaching including CpG oligonucleotides to enhance immune responses and does not cure the deficiencies of Malone, Barchfield, and Rappuoli.

None of the references alone or in combination provide any reason to arrive at Applicants' claimed subject matter. The Office Action has not made a *prima facie* case that claims 1 and 41 are obvious.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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